



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>5</sup> :</b> A61K 31/505, 31/415, 31/16 A61K 31/70, 31/195, 31/19 A61K 33/00, 9/00		<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/02148</b> <b>(43) International Publication Date:</b> 3 February 1994 (03.02.94)
<b>(21) International Application Number:</b> PCT/HU93/00016 <b>(22) International Filing Date:</b> 18 March 1993 (18.03.93)			<b>(74) Agent:</b> ADVOPATENT; P.O. Box 11, H-1251 Budapest (HU).
<b>(30) Priority data:</b> P 92 02398 22 July 1992 (22.07.92) HU			
<b>(71) Applicant (for all designated States except US):</b> VEPEX KFT. [HU/HU]; Nágyajtai út 2/b, H-1026 Budapest (HU).			
<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> HANGAY, György [HU/HU]; Pannónia u. 35-37, H-1136 Budapest (HU). OLÁH, Gáborné [HU/HU]; Kiss Áron u. 22/B, H-1125 Budapest (HU). TÓKOS, Edit [HU/HU]; Kárpát u. 26, H-1133 Budapest (HU). VÁMOS, György [HU/HU]; Zugligeti u. 50, H-1121 Budapest (HU).			

**(54) Title:** NOVEL BIOACTIVE COMPOSITIONS, PREPARATION AND USE THEREOF**(57) Abstract**

The invention relates to a pharmaceutical composition for treating and alleviating the symptoms of vulvitis and vulvovaginitis. The compositions according to the invention comprises 0.05-0.5 % by weight of folic acid, 0.25-2.5 % by weight of panthenol and/or 0.15-1.5 % by weight of allantoin, 0.75-7.5 % by weight of protein hydrolysate or casein hydrolysate, 3.0-15.0 % by weight of lactose or dextrose, 0.25-2.5 % by weight of lactic acid, 0.25-2.5 % by weight of magnesium sulfate and 0.75-7.5 % by weight of sodium chloride or ammonium chloride which are formulated in form of suppositories, ointments, solutions or sprays.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

NOVEL BIOACTIVE COMPOSITIONS, PREPARATION  
AND USE THEREOF

This invention relates to a new bioactive composition as well as the preparation and use thereof for treating the symptoms of vulvitis and vulvovaginitis (genital fluor).

The symptoms mentioned and their treatment raise a number of problems since the restoration of a health damage arising from the abnormal function of vagina is connected also with a rapid reconstitution or with the possibility of a rapid reconstitution of epithelium tissues and not only with curing the symptoms of the disease. The character of the treatment of genital fluor is discussed by Dr. S. Gardó in two papers entitled: "The Causes and Treatment of Genital Fluor" /Magyar Nőorvosok Lapja (Journal of Hungarian Gynecologists) 54, pp. 7-12 (1991)/ and: "The Treatment of Genital Fluor" /ibidem 54, pp., 187-191 (1991)/.

It is known that the development or reconstitution of the appropriate normal microflora of lactobacilli in the vagina contributes to the suppression of symptoms, however, there exists several possibilities and variations for restoring the normal state and the effect of these cannot uniformly be assured in each case.

In the Hungarian patent specification No. 190,732 about hundred ingredients are described (disclosed), nearly thirty combinations of which are suggested to prepare for

- 2 -

restoration of the normal microflora in the vagina. These combinations are aimed to achieve the same effect such as the increase in the germ number of lactobacilli or the restriction of pathogenic or pseudopathogenic micro-organisms, respectively however, several combinations had to be tested in a number of cases, the suppression of symptoms was lengthy from time to time or the combination did not show an adequate activity.

The assuring of absorption is also an important factor in the use of therapeutical products. According to the experience the traditional W/O and O/W type ointments and emulsions as well as aqueous or alcoholic (ethanolic) solutions do not promote and even inhibit the development of a suitable effect on treating the symptoms of vulvitis.

The present invention relates to a composition, which is in general useful for alleviating the symptoms of vulvitis and vulvovaginitis and exerts a regenerative and inuring effect, too on the epithelial tissues injured and/or irritated.

In an other aspect, the present invention relates to the stabilization and fast absorption of the composition.

For preparing the composition according to the invention comprises 0.05-0.5 % by weight of folic acid, 0.25-2.5 % by weight of d-panthenol, 0.15-1.5 % by weight of allantoin, 0.75-7.5 % by weight of protein hydrolysate or casein hydrolysate, 3.0-15.0

- 3 -

% by weight of lactose or dextrose, 0.25-2.5 % by weight of lactic acid, 0.25-2.5 % by weight of magnesium sulfate and 0.75-7.5 % by weight of sodium chloride or ammonium chloride mixed with a pharmaceutically acceptable carrier (vehicle) and/or auxiliaries (additives). A composition is formed being useful to treat vulvitis and vulvovaginitis or to alleviate the symptoms thereof. The composition may be in the form of a suppository ointment, solution or spray. Polyoxyethylene and polyoxyethylene sorbitan fatty acid esters are used as pharmaceutically acceptable carriers.

The suppositories contain 0.05-0.5 % by weight of folic acid, 0.8-1.5 % by weight of protein hydrolisate, 8-14 % by weight of lactose, 1.0-2.0 % by weight of lactic acid, 1.0-2.1 % by weight of magnesium sulfate, 2.0-4.0 % by weight of sodium chloride or ammonium chloride, 60.0-68.0 % by weight of polyoxyethylene 1540 and 10-15 % by weight of sorboxethene monolaurate. Practically, the suppositories weigh 3.5-4.0 g each.

The ointments contain 0.2 % by weight of d-panthenol, 0.75-1.5 % by weight of protein hydrolisate, 7-12.0 % by weight of lactose, 0.5-2.0 % by weight of lactic acid, 0.1-0.5 % by weight of magnesium sulfate, 6.0-10.0 % by weight of sorboxethene monolaurate, 25-70.0 % by weight of polyoxyethylene 400 and 0.5-51.0 % by weight of polyoxyethylene 1540.

- 4 -

The solutions or sprays, respectively contain 0.2-1.0 % by weight of d-panthenol, 0.6-2.0 % by weight of protein hydrolysate, 5.0-10.0 % by weight of lactose, 0.5-1.0 % by weight of lactic acid, 0.3-0.5 % by weight of magnesium sulfate, 2.0-3.0 + by weight of sodium chloride, 44.5-50.0 % by weight of polyoxyethylene 400, 7.5-12.0 % by weight of sorboxethene monolaurate, optionally polyoxyethylene 4000 or 1540 as well as 19.0-33 % by weight of distilled water.

The compositions are stable. As evidenced by biological experiments, they alleviate the symptoms of most various types of vaginitis and vulvitis and promote the recovery or the suppression of symptoms. An important advantage of the compositions appears therein that their use do not require any examination depending on the condition of the patient since they can commonly be used in the formulations mentioned above.

Thus, the compositions comprising the ingredients according to the invention are useful to normalize the vaginal flora, to reconstitute the microflora injured, to regenerate and inure the epithelial tissues as well as to provide a preventive (prophylactic) protection against vaginal infections.

Among the sorts of vitamin B folic acid proved to be most effective, but the determination of their suitable doses (0.001-0.1 g for each dose) or concentrations (0.03-0.3

- 5 -

%), respectively are also important. The use of d-panthenol in a concentration of 0.5-2 % (0.2-1.3 g for each dose) is also preferred.

According to our findings protein hydrolysate or casein hydrolysate are equally suitable nitrogen sources since the stability can be assured in all three cases. Lactose and in several cases dextrose are useful carbon sources.

The presence of some ions and trace elements in the "composition" is also essential. Among the cations  $\text{Na}^+$ ,  $\text{NH}_4^+$  and  $\text{Hg}^{2+}$ , among the anions  $\text{Cl}^-$  and  $\text{SO}_4^{2-}$  proved to be most important. Accordingly, sodium chloride and/or ammonium chloride as well as magnesium sulfate have been employed. The adjustment of pH values (to 2-3.5) and optimum concentrations (to 0.1-0.5 %) of the products are of great importance. First above all, d-panthenol, allantoin and folic acid are suitable to treat the irritative symptoms occurring in consequence of the diseases and epithelial injuries of various levels: the water balance of sugars and human tissues can be reconstituted by them. Lactic acid is conveniently administered to achieve an astringent effect.

The activity of the composition is considerably depending on the formulation and selection of the preferably pharmaceutical form. Suppository, gel and solution or spray are advantageous forms. Surprisingly, the formulating materials (additives) of compositions of the invention

- 6 -

increased the activity and insured the physical-chemical and microbiological stability of combinations of the active ingredients to a greater degree than expected.

According to our experience, the advantages of suppository masses (base) containing polyoxyethylene and polyoxyethylene fatty acid ester(s) are as follows:

- a greater uptake of water and powdered materials,
- establishment of an optional consistency by mixing the variants of diverse molecular weights, as well as
- an enhanced stability of the suppository mass (base) and active ingredients incorporated therein.

Polyoxyethylene stearate (Mirj<sup>R</sup>), sorbitan esters, e.g. sorbitan monolaurate (Span 20<sup>R</sup>) or sorboxethene esters, such as sorboxethene monolaurate (Tween 20<sup>R</sup>) as well as sorboxethene monooleate (Tween 90<sup>R</sup>) may be mentioned as examples of polyoxyethylene esters.

The combinations listed hereinafter proved to be most successful:

	I	II
Sorboxethene monolaurate	15-20 %	-
Polyoxethylene stearate	-	5-10 %
Polyoxethylene glycole		
1540	75-85 %	90-95 %

The suppository mass (base) enhanced the activity of bioactive materials since the hygroscopicity of mass (base) is a factor increasing the effect, whereby the complete

- 7 -

dissolution of active ingredients is promoted through an increase in the volume of vaginal fluid. In addition, the suppositories exert a sustained action (a few hours in vivo) due to the slow disintegration.

An other advantage of the suppository mass (base) appears therein that it makes possible to preserve stable a microbiologically unstable system.

The gel form provides advantages being similar to those of suppositories. One type of two different gels contains about 50 % of polyoxyethylene glycole 1540 and 30-35 % of polyoxyethylene glycole 400, whereas the other type contains polyoxyethylene glycole 400 in its major part and only 1-2 % of polyoxyethylene glycole 1540. (Macrogel)

For preparing compositions formulated in the form of solutions, optionally as mechanical sprays the ingredients, taken in amount depending on the total weight, are dissolved in the aqueous phase, polyoxyethylene glycole 400 and water, then polyoxyethylene glycole 1540 and 4000 are added.

The invention is illustrated in detail by the following Examples.

- 8 -

Example 1  
Suppository

Ingredients	Composition % by weight	
	1	2
Folic acid	0.05	0.2
Allantoin	-	0.5
Protein hydrolysate	1.25	0.8
Lactose	14.0	8.0
Lactic acid	2.0	1.0
Magnesium sulfate	1.4	1.0
Sodium chloride	4.0	2.0
Polyoxyethylene glycole 1540	63.0	66.5
Polyoxyethylene- sorbitan mono- laurate	14.3	15.0
Polyoxethylene- sorbitane mono- stearate	-	5.0

Note: The percentages given above refer to suppositories weighing 3.5-4.0 g each

The suppositories are prepared as follows:

After mixing folic acid with an adequate amount of lactose, the remainder of lactose, magnesium sulfate and sodium chloride are successively added while stirring. Protein hydrolysate is immediately mixed to the powder mixture before preparing the suspension.

- 9 -

Simultaneously, after melting the polyoxyethylene glycole and polyoxyethylene glycole fatty acid esters and reaching a temperature of 60 °C, lactic acid is mixed to the melt, the powder mixture is suspended in the liquid suppository base containing lactic acid, then the mass is homogenized in a colloid mill. At a temperature of about 55 °C, the mass is filled into cooled moulds.

Example 2

Ointment

Ingredients	Composition % by weight	
	3	4
d-Panthenol	1.0	0.5
Protein hydrolysate	1.0	0.75
Lactose	7.0	12.0
Lactic acid	0.5	1.0
Magnesium sulfate	0.5	0.5
Polyoxyethylene-sorbitan monolaurate	6.0	10.0
Polyoxyethylene glycole 400	31.0	25.75
Polyoxyethylene glycole 1540	51.0	42.0
Condensate of hydrogenated castor oil with ethylene oxide (40 moles)	-	3.5

- 10 -

After cooling to about 50 °C the melt of polyoxyethylene glycole and polyoxethylene-glycole fatty acid esters, optionally a condensate of hydrogenated castor oil with ethylene oxide, panthenol is firstly dissolved in the melt and after cooling the mass further to 40-45 °C, the powder materials appropriately milled (to a sieve size of VI) and previously mixed together are suspended therein. Finally, lactic acid is mixed thereto and the system is stirred until the complete cooling down.

Example 3

Solution or spray.

Ingredients	Composition % by weight	
	5	6
d-Panthenol	0.2	1.0
Protein hydrolysate	0.6	2.0
Lactose	5.0	10.0
Lactic acid	0.5	0.5
Magnesium sulfate	0.5	0.3
Sodium chloride	2.0	3.0
Allantoin	-	0.2
Polyoxyethylene-glycole 400	46.5	49.5
Polyoxyethylene-sorbitan monolaurate	12.0	7.5
Polyoxyethylene-sorbitan monooleate	-	2.0
Distilled water	32.7	24.0

- 11 -

The powdered ingredients and panthenol are successively portionwise added to the distilled water warmed to a temperature of about 60 °C. Simultaneously, the ingredients of the "fatty phase" are melted. The two phases are mixed at a temperature of about 60 °C and stirred then until it cools down.

Example 4

The clinical investigation of suppositories according to Example 1 was simultaneously carried out in the Department of Obstetrics and Gynecology of the Semmelweis Medical University (SOTE) Budapest, Hungary as well as in the Department of Obstetrics and Gynecology of the Szent-Györgyi Albert Medical University (SZOTE) Szeged, Hungary. The clinical examinations were aimed to determine the effectiveness of the suppositories and to prove that the efficiency of the treatment reached or exceeded the efficiency level of the standard treatment used in the gynecology.

The complex trial was extended to the so-called purity examination of the vagina, cultivation of bacteria and fungi, as well as to the colposcopic and cytologic tests, bimanual gynecologic examination, determination of the pH values and evaluation of subjectively judged complaints. A significant change under effect of the treatment was stated in the pH values of the persons examined. The changes in the cervix, vagina and vulva were evaluated on basis of the trial of SOTE before and after the treatment. The results are summarized in Table I.

- 12 -

Table I  
Changes in the pH values on effect of treatment

Treatment	Before treatment			After treatment		
	Cervix	Vagina	Vulva	Cervix	Vagina	Vulva
Suppository of inven- tion	5.00 <sub>+</sub> 0.50	4.77 <sub>+</sub> 0.64	4.85 <sub>+</sub> 0.69	4.59 <sub>+</sub> 0.47	4.42 <sub>+</sub> 0.60	4.27 <sub>+</sub> 0.60
Standard treatment	4.82 <sub>+</sub> 0.59	4.69 <sub>+</sub> 0.60	4.70 <sub>+</sub> 0.54	4.52 <sub>+</sub> 0.58	4.39 <sub>+</sub> 0.58	4.35 <sub>+</sub> 0.67

- 13 -

It is obvious from the results that the pH values were shifted to negative direction by the suppository of the invention at all the three sites of the examinations.

It has to be considered on the evaluation that the carrying-out of the (standard) treatment known in the art requires complicated, circuitous and professional instructions for the patient.

The examinations of SZOTE were aimed to control the vagina. These results are summarized in Table II. The results of check examinations performed by one month following the treatment are also shown in column 3 of Table II.

Table II

Changes in the pH values immediately and by one month, respectively after treatment

Treatment	Before treatment	Immediately after treatment	By 1 month after treatment
Suppository of the invention	5.87 $\pm$ 0.98	5.28 $\pm$ 0.65	5.43 $\pm$ 0.25
Standard treatment	6.48 $\pm$ 1.33	5.47 $\pm$ 0.66	6.07 $\pm$ 0.61

The effectivity of the suppository is proved also by the results of Table II. The

-14 -

duration of effect shows significant differences from the (standard) method of treatment known in the art.

The development of subjective complaints is illustrated in Table III on basis of the examinations of SOTE. The four syndromes, i.e. irritation, pain, rubor and discharge were evaluated both by the patients and physicians concerned.

The severity of syndromes was expressed by the following score:

0 = free from complaints; 1 = mild complaints;  
2 = moderate complaints; 3 = severe complaints.

- 15 -

Table III  
Evaluation by scoring the subjective parameters

Syndrome	Suppository				(Traditional) treatment known in the art			
	Before treatment		after treatment		before treatment		after treatment	
	patient	physician	patient	physician	patient	physician	patient	physician
<b>Irritation</b>								
0	8	20	24	26	7	20	15	22
1	17	7	3	1	12	4	12	5
2	2	-	-	-	8	3	-	-
3	-	-	-	-	-	-	-	-
<b>Pain</b>								
0	19	-	26	-	15	-	25	-
1	6	-	1	-	12	-	2	-
2	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-
<b>Discharge</b>								
0	4	1	5	6	2	3	6	4
1	-	1	19	15	1	1	16	14
2	20	20	2	4	15	19	5	9
3	3	3	1	-	9	5	-	-
<b>Rubor</b>								
0	1	3	14	13	2	4	13	11
1	16	12	13	12	13	10	13	13
2	10	12	-	2	11	13	1	3
3	-	-	-	-	1	-	-	-

- 16 -

It can be pointed out in relation to the subjective complaints that the improvement in all the four syndromes, especially in the cases of irritation, pain and discharge was significant. A significant alleviation of complaints was observed by the joint evaluation of complaints.

- 17 -

C l a i m s

1. A pharmaceutical composition for treating the symptoms of vulvitis or vulvovaginitis, which comprises 0.05-0.5 % by weight of folic acid, 0.25-2.5 % by weight of panthenol and/or 0.15-1.5 % by weight of allantoin, 0.75-7.5 % by weight of protein hydrolisate or casein hydrolisate, 3.0-15.0 % by weight of lactose or dextrose, 0.25-2.5 % by weight of lactic acid, 0.25-2.5 % by weight of magnesium sulfate and 0.75-7.5 % by weight of sodium chloride or ammonium chloride in an admixture with a pharmaceutically acceptable carrier and/or auxiliary substances.

2. A composition as claimed in claim 1, which comprises polyoxyethylene glycole and polyoxyethylene sorbitan fatty acid ester as pharmaceutically acceptable carriers.

3. A suppository composition as claimed in claim 1, which comprises 0.05-0.1 % by weight of folic acid, 0.8-1.5 % by weight of protein hydrolisate, 8-14 % by weight of lactose, 1.0-2.0 % by weight of lactic acid, 1.0-2.1 % by weight of magnesium sulfate, 2.0-4.0 % by weight of sodium chloride or ammonium chloride, 60.0-68.0 % by weight of polyoxyethylene-glycole 1540 and 10-15 % by weight of polyoxyethylene-glycole monolaurate.

4. An ointment composition as claimed in claim 1, which comprises 0.2 % by weight of d-panthenol, 0.75-1.5 % by weight of protein

- 18 -

hydrolisate, 7-12.0 % by weight of lactose, 0.5-2.0 % by weight of lactic acid, 0.1-0.5 % by weight of magnesium sulfate, 6.0-10.0 % by weight of polyoxyethylene glycole monolaurate, 25-70.0 % by weight of polyoxyethylene glycole 400 and 0.5-51.0 % by weight of polyoxyethylene glycole 1540.

5. A solution or spray composition as claimed in claim 1, which comprises 0.2-1.0 % by weight of d-panthenol, 0.6-2.0 % by weight of protein hydrolisate, 5.0-10.0 % by weight of lactose, 0.5-1.0 % by weight of lactic acid, 0.3-0.5 % by weight of magnesium sulfate, 2.0-3.0 % by weight of sodium chloride, 44.5-50.0 % by weight of polyoxyethylene glycole 400, 7.5-12.0 % by weight of polyoxyethylene-glycole monolaurate as well as 19.0-33 % by weight of distilled water.

6. A process for the preparation of a pharmaceutical composition, which comprises mixing 0.05-0.5 % by weight of folic acid, 0.25-2.5 % by weight of panthenol and/or 0.15-1.5 % by weight of allantoin, 0.75-7.5 % by weight of protein hydrolisate or casein hydrolisate, 3.0-15.0 % by weight of lactose or dextrose, 0.25-2.5 % by weight of lactic acid, 0.25-2.5 % by weight of magnesium sulfate and 0.75-7.5 % by weight of sodium chloride or ammonium chloride with a pharmaceutically acceptable carrier and/or auxiliary substances and forming the mixture to a suppository, ointment, solution or spray, respectively being useful

- 19 -

for the treatment or alleviation of symptoms of vulvovaginitis or vulvitis.

7. A process as claimed in claim 6, which comprises using polyoxyethylene-glycole or polyoxyethylene-glycole sorbitan fatty acid ester as pharmaceutically acceptable carriers.

8. Method for the treatment of symptoms of vulvovaginitis and vulvitis as well as prevention (prophylaxis) of such health damage, characterized by administering the patient a composition according to any of the claims 1-3 suitably in the form of suppositories in a daily dose of 3.5-4.0 g.

9. Use of a composition according to any of the claims 1-5 for alleviating the symptoms of vulvitis and vulvovaginitis or for preventing such injury.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/HU 93/00016

## A. CLASSIFICATION OF SUBJECT MATTER

IPC<sup>5</sup>: A 61 K 31/505, 31/415, 31/16, 31/70, 31/195, 31/19, 33/00, 9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC<sup>5</sup>: A 61 K 31/505, 31/00, 33/00, 9/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	B. Helwig, H. Helwig "Moderne Arzneimittel", fifth edition, published 1980, by Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, pages 762-765, 770, 1459, especially products "Albothyl® Flour-Tabletten", "Colpan®", "Edd® Oestrogen", "Globichthol®", "Gyan®", "Gynaedron®", "Gynichtherm®", "Gynichthol®", "Tampovagan® c.Acid.lact.5 %", "Bepanthen® Roche Vaginal-tabletten", "Bepanthen® Salbe".	1,3-6
A	H. Janistyn "Handbuch der Kosmetika und Riechstoffe", volume III, published 1973, by Dr. Alfred Hüthig Verlag Heidelberg, pages 950-956, chapter "Intimkosmetik", especially page 952, lines 6-20; page 954, no. 3; page 955, paragraph 3., Intim-Cremes.	1,2,4-7
A	US, A, 4 393 066 (D.M. GARETT, W.R. ROBIN) 12 July 1983 (12.07.83), column 2, lines 22-26; column 3, lines 12-63.	1,3,6
A	WO, A1, 88/04 927 (DAVIRAND, INC.) 14 July 1988 (14.07.88), abstract; claims 1-7,19; page 5, lines 29-35,	1-3,6,7

 Further documents are listed in the continuation of Box C. See patent family annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

16 June 1993 (16.06.93)

29 June 1993 (29.06.93)

Name and mailing address of the ISA/ AT  
AUSTRIAN PATENT OFFICE  
Kohlmarkt 8-10  
A-1014 Vienna  
Facsimile No. 0222/53424/535

Authorized officer

Mazzucco e.h.

Telephone No. 0222/5337058/33

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/HU 93/00016

## C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	page 7, lines 11-26; page 9, lines 26-34; page 10, lines 2-10.  GB, A, 1 368 201 (COMPREHENSIVE PHARMACEUTICALS LIMITED) 25 September 1974 (25.09.74), claims 1-5; page 2, lines 62-69; page 3, lines 18-29; examples 4-6. -----	1,2,6,7

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/HU 93/00016

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 8, 9  
because they relate to subject matter not required to be searched by this Authority, namely:  
See PCT rule 39.1 (iv).  
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.



No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.

PCT/HU 93/00016

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A 4393066	12-07-83	keine - none - rien	
WO A1 8804927	14-07-88	keine - none - rien	
GB A 1368201	25-09-74	BE A1 778334 CA A1 963388 DE A 2202964 FR A6 2122613 FR B2 2122613 IE B 35991 ZA A 7200423	16-05-72 25-02-75 10-08-72 01-09-72 01-08-75 21-07-76 25-10-72